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Mathematical Analysis of the Accuracy of the Evaluation Criterion X in Patients with COVID-19 Infection

Vladimir T. Ivashkin[1*], Evgeniya Y. Medvedeva[1], Vladimir M. Nechaev[1], Irina R. Popova[1], Manana R. Shirtladze[1], Yuliya O. Shulpekova[1], Aleksandr A. Simushev[2] and Sakhavet M. Zarbaliev[2]

[1]Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

[2]Department of Mathematical and Computer Modelling, National Research University, Moscow, Russian Federation

Abstract

Prognostic criterion X is calculated using an equation that includes 7 indexed parameters (age and body temperature of the patient, oxygen saturation ($SatO_2$), number of blood neutrophils, values of creatinine, C-reactive protein and blood creatinine). Criterion X is measured in points, the number of which is directly proportional to the severity of the disease. The accuracy of criterion X was estimated by the method of ordinary least squares regression (OLS regression) and correlation analysis according to the criteria of r Pearson and r_s Spearman in 305 patients with COVID-19 infection and pneumonia. The data obtained were compared by assessing the severity of the disease according to the general clinical parameters X_{cl} (state of consciousness, body T °C, pulse and respiratory rate per minute) and the NEWS-2 criterion. The results of the OLS regression demonstrate that there is a strong linear relationship between X_{cl} and X (X_{ev}) (linear regression coefficient β_1 = 0.8057, the standard deviation (std) of the coefficient β_1 is s_1 = 0.022). The coefficient of determination of this regression is R^2 = 0.821. This means that the assessment of the severity of the disease and its prognosis for X_{cl} and X coincide with each other in 82% of cases. A comparison of the criteria X (X_{ev}) and X_{NEWS-2} indicates the absence of a linear relationship between them (the value of the linear regression coefficient β_1= 0.0553. The std of the coefficient β_1 is s_1 = 0.002). The comparison of the X_{cl} and X_{NEWS-2} criteria was not carried out due to the lack of data in the public domain. The evaluation criterion X meets the necessary statistical requirements and can be used to objectively assess the severity of inflammatory diseases, as well as to develop treatment regimens.

Keywords: COVID-19 infection, SARS-CoV-2-pneumonia, Criterion X, NEWS-2 scale, Early warning scores, Indexed laboratory parameters

***Correspondence to:** Vladimir T. Ivashkin, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation.

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Introduction

The most important condition for the effective treatment of any disease is an accurate assessment of its severity, which makes it possible not only to predict possible complications in a timely manner and achieve complete recovery (clinical remission), but also minimize side effects. All modern therapeutic regimens have been created with this requirement in mind. The existing evaluation criteria (APACHE III, SAPS II, DTEWS, MEWS, NEWS-2) are quite sensitive, but highly specialized and difficult to reproduce [1-5]. In addition, they contain parameters that are often poorly correlated with each other, namely: respirations per minute, systolic blood pressure, and level of consciousness. This circumstance reduces their evaluative value.

The gated recurrent unit prognostic model is also used. It is based on a recurrent neural network architecture and takes into account gender, height, weight, comorbidity according to the Charlson scale, body temperature, blood pressure, $SatO_2$, the presence of chronic kidney disease and diabetes mellitus, and blood test data (a total of 48 evaluation parameters) [6]. This model requires a powerful laboratory base and is designed primarily to predict mortality, rather than the severity of the patient's condition at the initial stage of treatment. We have developed a new evaluation criterion X, which takes into account not only clinical parameters but also indexed laboratory parameters that systematically characterize the condition of the body [7]. These parameters are interrelated. This approach enhances the value of criterion X, but it requires mathematical validation. Criterion X is intended for selecting effective treatment and assessing prognosis. Mathematical analysis of the accuracy of the evaluation criterion X ($X_{ev} = X_{evaluation}$).

Materials and Method

At the University Clinical Hospital No. 2 of the First Moscow State Medical University named after I.M. Sechenov, 305 patients with COVID-19 infection and pneumonia were examined. In this group, there were 135 (44%) men aged 29 to 92 years (mean age 62 years) and 170 (56%) women aged 23 to 95 years (mean age 68 years). The diagnosis of pneumonia was confirmed by computed tomography, and COVID-19 infection was confirmed by polymerase chain reaction results from a throat swab. Upon admission and during observation, the severity of the patients' condition was assessed according to general clinical criteria $X_{clinical-rating}$ ($X_{cl} = X_{clinical}$)) (level of consciousness, patient position in bed, body temperature, heart rate, number of breaths per minute), the NEWS-2 scale [1], as well the evaluation criterion (X_{ev}) previously proposed by us, calculated according to the equation based on the indexed parameters presented in table 1 [8]. These parameters (Table 1) were assessed on the first day of hospitalization before treatment began.

It should be noted that $SatO_2$ is negatively correlated with the severity of the patient's condition. The lower the $SatO_2$, the more severe the condition. Using the directly measured $SatO_2$ values in equation is incorrect, since it results in a decrease in the value of the criterion X, which is directly proportional to the severity of the disease. To resolve this contradiction, the parameter "corrected $SatO_2$" (KS) was introduced. The calculation method is as follows: the possible values of $SatO_2$ range from 56 to 100%. At $SatO_2$ falls below 60%, a hypoxemic coma with a fatal outcome occurs. This range is divided into intervals with a step of 5, for each of which a median value is determined (Table 2). The median values of $SatO_2$ for each interval are multiplied by 8 ($SatO_2$ index), and the resulting products are arranged in reverse order (column 4 in table 2). This is the sought-after KS. The logical contradiction is resolved: the smaller the KS, the smaller the value of X. Below equation for calculating the point criterion for assessing the severity of the disease [2]:

$$X = 0.01 \times (16B + 6T^{\circ} + KS + 13N + 16K + 26C + 15F)$$

Where, X is the number of calculated points characterizing the severity of the patient's condition; the coefficient 0.01 is a value expressed in the form of a decimal, equal to one divided by the sum of the indices of all estimated parameters (in this case, it is equal to 100); the values of the indices and the names of all the evaluation parameters are provided in parenthesis. The value KS is taken from column 4 of table 2.

Example of criterion calculation X

Patient D, 48 years old, body temperature = 36.6 °C, $SatO_2$ = 96%, neutrophils = 44.2%, blood creatinine = 78.6 μmol/l, C-reactive protein = 1.67 mg/l, fibrinogen = 2.85 g/L. Let's calculate the value of criterion X using below equation:

$$X = 0.01 \times (16 \times 48 + 6 \times 36.6 + 464 + 13 \times 44.2 + 16 \times 78.6 + 26 \times 1.67 + 15 \times 2.85) = 34.30 \approx 34 \text{ points}$$

Where, $X \leq 40$ points indicate a mild form of the disease (L); $41 \leq X \leq 63$ indicates a moderate form of the disease (MT); $X > 63$ indicates a severe form of the disease (T) [2].

The accuracy of criterion X was assessed using OLS regression, which is based on the assumption of a linear relationship between the independent and dependent variable [3-5, 7, 8]. OLS allows the creation of a model for predicting and analyzing the influence of features on the target variable. The equation for linear regression is as follows:

$$Y = \beta + \beta_x$$

Where, y is the predicted dependent variable, x is the independent variable, and β_0 and β_1 are the regression coefficients.

The search for optimal values β_0 and β_1, which minimize the sum of squared errors, was performed using OLS in the Python 3.12 environment for the quantitative prediction of criterion X. For this, we introduced the values X_{ev}, X_{cl} and digitized the severity of the disease: 0 (mild disease course [L]), 1 (moderate disease course [MT]), and 2 (severe disease course [T]).

Through correlation analysis, the Pearson correlation coefficients r between the evaluation parameters (located in table 3 and table 4 at the intersection of row and column names) were determined. It is

Table 1: List and values of indices of estimated parameters.

Parameter	Age (years)	Body (T°)	$SatO_2$ (%)	Neutrophils (%)	Blood creatinine (μmol/l)	CRP (mg/l)	Fibrinogen (g/l)
Index	16	6	8	13	16	26	15

Table 2: Principle of calculation of KS.

$SatO_2$ (%)	Median interval (%)	Direct KS (points)	Sought-after KS (points)
96 - 100	98	784	464
91 - 95	93	744	504
86 - 90	88	704	544
81 - 85	83	664	584
76 - 80	78	624	624
71 - 75	73	584	664
66 - 70	68	544	704
61 - 65	63	504	744
56 - 60	58	464	784

Table 3: Correlation matrix of estimated parameters (Pearson's r coefficient).

Pearson's r coefficient	B	T°	S	N	K	C	F	NEWS-2	X
B	1.00	-0.11	0.06	0.22	0.15	0.12	0.00	-0.12	0.31
T°	-0.11	1.00	0.03	0.06	0.06	0.14	0.03	-0.04	0.13
S	0.06	0.03	1.00	0.03	0.00	-0.01	-0.06	0.17	0.05
N	0.22	0.06	0.03	1.00	0.13	0.38	0.28	0.01	0.50
K	0.15	0.06	0.00	0.13	1.00	0.09	0.02	-0.01	0.38
C	0.12	0.14	-0.01	0.38	0.09	1.00	0.55	0.04	0.93
F	0.00	0.03	-0.06	0.28	0.02	0.55	1.00	0.05	0.51
NEWS-2	-0.12	-0.04	0.17	0.01	-0.01	0.04	0.05	1.00	0.02
X	0.31	0.13	0.05	0.50	0.38	0.93	0.51	0.02	1.00

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evident that the correlation coefficient of a random variable with itself is 1, so the diagonal elements are marked with the number 1. The result is presented in table 3 and table 4 where the numbers in the cells are the values of the standard Pearson's correlation coefficients r; $0.01 \leq r \leq 0.29$ is a weak positive relationship; $0.30 \leq r \leq 0.69$ is a moderate positive relationship; $0.70 \leq r \leq 1.00$ is a strong positive relationship; $-0.29 \leq r \leq -0.01$ is a weak negative relationship; $-0.69 \leq r \leq -0.30$ is a moderate negative relationship; and $-1.00 \leq r \leq -0.70$ is a strong negative relationship [9].

Spearman's rank correlation coefficients r_s are calculated separately (Table 5). A moderate positive correlation of a high degree of significance between X_{ev} and X_{cl} (Pearson's r = 0.34 with a significance level of $\alpha \leq 0.001$) was revealed.

In table 6, a moderate positive association of high significance between X_{ev} and X_{cl} (Spearman's r_s = 0.33 at the significance level$\alpha \leq 0.001$) was revealed.

Thus, the use of Pearson's r and Spearman's r_s correlation coefficients to assess the correlation X_{ev} and X_{cl} yielded almost identical results (0.34 and 0.33, respectively). We predict the values of the dependent variable from the independent variables. The results of the OLS regression of the form $X_{cl} = \beta_1 X_{ev}$ are presented in table 6. This table represents a regression report between the dependent variable X_{cl}, which is determined by the clinical criteria, and the independent variable $X = X_{ev}$, which is calculated according to equation. The results of the econometric study show that the regression coefficient β_1= 0.8057 (indicating a strong linear dependence). The std of the coefficient β_1 is s_1 = 0.022. The coefficient of determination for this regression is R^2 = 0.821.

The following linear regression was performed: $X_{cl} = \beta_0 + \beta_1 X_{ev}$, where X_{cl} is the dependent variable determined by general clinical criteria, and $X = X_{ev}$ is the independent variable calculated according to equation. The results of the econometric study show that the values of the regression coefficients β_0 and β_1 are 0.76 and 0.31, respectively. The std of the coefficient β_0 is s_0 = 0.7, and the std of the coefficient β_1 is s_1= 0.31. The coefficient of determination for this regression is R^2 = 0.17.

Next, a linear regression was performed: $X_{ev} = \beta_1 X_{cl}$, where X_{ev} is the dependent variable calculated according to equation, and X_{cl} is the independent variable determined by general clinical criteria. The econometric study reveals the regression coefficient β_1 = 1.0192. The std of the coefficient β_1 is s_1 = 0.027. The coefficient of determination for this regression is R^2 = 0.821. A further linear regression was constructed: $X_{ev} = \beta_1 X_{NEWS\text{-}2}$, where X_{ev} is the dependent variable calculated according to equation, and $X_{NEWS\text{-}2}$ is the independent variable determined by the NEWS-2 table 1. The econometric study shows the value of the regression coefficient: β_1 = 0,0553. The std of the coefficient β_1 is s_1= 0.002. The coefficient of determination for this regression is R^2 = 0.768.

Discussion

In modern clinical medicine, various assessment criteria and scales are widely used. For determining the severity of patients with COVID-19 infection, the NEWS-2 scale is employed. It is objective and convenient; however, its methodology and calculation equation were not found in the open sources. The assessment criterion X proposed by us is transparent and, importantly, is based on the use of routine laboratory parameters, each of which can be measured with great accuracy. To determine the value of the X-criterion, seven parameters were used, measured exclusively empirically, rather than calculated using equations or table 1 to table 6. Thus, when calculating the mortality rate, the Charlson comorbidity index, taken from a special figure 1, is used. This is an "index within an index" situation. In this study, we analyzed the assessment accuracy of criterion X using the Pearson correlation coefficient r, Spearman's rank correlation coefficient r_s, and the results of OLS regression [10].

The standard Pearson correlation coefficient r is highly sensitive to data outliers (rejections) that arise from erroneous measurements

Table 4: Descriptive statistics of estimated parameters.

Parameters	B	K	X	NEWS-2	X_{ev}	X_{cl}
Count	305	305	305	305	305	305
Mean	65	98.44	59.53	3.39	1.27	1.17
Std	15	27.56	16.33	1.92	0.57	0.42
Min	23	62.7	29	0	0	0
25%	55	80.3	47	2	1	1
50%	66	92.4	56	3	1	1
75%	77	109.32	68	4	2	1
Max	95	306.51	119	12	2	2

Note: Count is the number of elements, 25%; 50%; and 75% are the corresponding quantiles.

Table 5: Correlation matrix for assessing the condition of patients (Pearson's criterion r).

Pearson's criterion	X	NEWS-2	X_{ev}	X_{cl}
X	1.00	0.28	0.83	0.34
NEWS-2	0.28	1.00	0.25	0.28
X_{ev}	0.83	0.25	1.00	**0.34**
X_{cl}	0.32	0.25	0.34	1.00

Table 6: Correlation matrix of patient condition evaluation (Spearman's r_s coefficient).

Pearson's criterion	X	NEWS-2	X_{ev}	X_{cl}
X	1.00	0.30	0.86	0.34
NEWS-2	0.30	1.00	0.24	0.25
X_{ev}	0.86	0.24	1.00	**0.33**
X_{cl}	0.34	0.25	0.33	1.00

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```
                            OLS Regression Results
=======================================================================================
Dep. Variable:               x_clinic   R-squared (uncentered):                   0.821
Model:                            OLS   Adj. R-squared (uncentered):              0.821
Method:                 Least Squares   F-statistic:                              1397.
Date:                Fri, 30 Sep 2022   Prob (F-statistic):                   1.12e-115
Time:                        12:53:52   Log-Likelihood:                         -235.51
No. Observations:                 305   AIC:                                      473.0
Df Residuals:                     304   BIC:                                      476.7
Df Model:                           1
Covariance Type:            nonrobust
===============================================================================
                  coef    std err          t      P>|t|      [0.025      0.975]
-------------------------------------------------------------------------------
x_valuation     0.8057      0.022     37.371      0.000       0.763       0.848
==============================================================================
Omnibus:                        0.769   Durbin-Watson:                   1.867
Prob(Omnibus):                  0.681   Jarque-Bera (JB):                0.793
Skew:                           0.120   Prob(JB):                        0.673
Kurtosis:                       2.933   Cond. No.                         1.00
==============================================================================
```

Figure 1: OLS regression results of the form $X_{cl} = \beta_1 X_{ev}$.

or inherently incorrect results, such as a negative body temperature value or an input error due to a decimal point. Even a single outlier can significantly affect the correlation coefficient, potentially changing its sign. In this regard, Spearman's rank correlation coefficient r_s is less sensitive. However, linear correlations tend to be more accurate than rank-based correlations. Ranking values when using r_s naturally reduces the measure of individual variability in the data [11].

The choice of correlation coefficient depends on two key principles and the specific characteristics of the relationship between the data. The Pearson correlation coefficient r is used when the data follows a normal distribution, and the sample size is large ($n \geq 30$). The Spearman rank correlation coefficient r_s is applied when the data is not normally distributed and the sample size is small ($n \leq 30$). In cases where $n \geq 30$ but the data distribution is not normal, the Spearman rank correlation coefficient is preferred. To obtain the most reliable results, both coefficients were used in our study, and their values were nearly identical (0.34 and 0.33).

The results of the OLS regression in the form of $X_{cl} = \beta_1 X_{ev}$ indicate a strong linear relationship ($\beta_1 = 0.8057$). The coefficient of determination $R^2 = 0.821$ shows that the regression equation $X_{cl} = \beta_1 X_{ev}$ explains 82.1% of the variance of the dependent variable, with the remaining 17.9% attributed to other factors. The adjusted R^2 equals 0.821, which indicates a high degree of fit, further confirming that the OLS model explains 82.1% of the variance in the dependent variable X_{cl}. There is no need to add additional variables to improve the model fit. The statistical hypothesis test for the significance of the regression coefficients, using the Fisher test, shows a high statistical significance (significance level $\alpha \leq 0.001$) for the overall regression and the strength of the relationship. The statistical significance of the correlation coefficient, the regression equation, and the β_1 parameter with respect to X_{ev} suggests that statistical predictions can be made using the derived regression equation.

$$X_{cl} = \beta_1 X_{ev}$$

The results of the OLS regression in the form $X_{ev} = \beta_1 X_{NEWS\text{-}2}$ indicate a weak linear relationship ($\beta_1 = 0.0553$). The coefficient of determination $R^2 = 0.768$ shows that the regression equation explains 76.8% of the variance in this dependent variable. However, independent verification is not possible in this case due to the lack of data in open sources.

Conclusion

The evaluation criterion X meets the necessary statistical requirements. The evaluation criterion X can be used for the objective assessment of the severity of acute inflammatory diseases, as well as for the development of treatment protocols that take into account the severity of patients' conditions.

Acknowledgements

None.

Conflict of Interest

None.

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